DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: SEP 05 2002

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	DHA GOLD® Golden Algae
Firm:	OmegaTech , Inc.
Date Received by FDA:	December 13, 2001
90-Day Date:	March 13, 2002

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 as soon as possible since it is past the 90-day date. Thank you for your assistance.

Felicia B. Satchell

Felicia B. Satchell

Attachments

95S-0316

RPT 110

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

DEC 2 4 2001

Sam Zeller, Ph.D.
OmegaTech Inc
4909 Nautilus Court North Suite 208
Boulder, Colorado 80301-3242

Dear Dr. Zeller:

This is to inform you that the notification, dated December 6, 2001, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on December 13, 2001. Your notification concerns the substance called "DHA GOLD® Golden Algae" that you assert is a new dietary ingredient.

In accordance with 21 C.F.R § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., February 26, 2002), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "DHA GOLD® Golden Algae."

Please note that acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After March 13, 2002, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Please contact us at (301) 436-2371, if you have any questions concerning this matter.

Sincerely yours,

Gary Coody

Gary Coody, R.Ph.
Acting Team Leader
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

OmegaTech™

December 6, 2001

Notification of a New Dietary Ingredient

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
200 C Street, SW
Washington, DC 20204

To the Food and Drug Administration:

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 U.S.C. §350b (a) (2), and consistent with the new final regulations published by the FDA in the Federal Register of September 23, 1997 (62 Fed. Reg. 49886-49892), 21 C.F.R. §109.6, "Requirements for premarket notification," OmegaTech hereby submits the following information concerning a new dietary ingredient that OmegaTech intends to begin marketing for use in dietary supplements. Pursuant to the applicable provisions of the DSHEA, 21 U.S.C. §350b (a) (2), OmegaTech will not introduce this new dietary ingredient into interstate commerce until at least 75 days after the date on which FDA receives this notification.

(1) NAME AND ADDRESS OF MANUFACTURER

The name and complete address of the manufacturer of the new dietary ingredient is as follows:

Manufacturer:
OmegaTech Inc.
4909 Nautilus Court N. Suite 208
Boulder, CO 80301-3242

Direct Correspondence to:
Sam Zeller, Ph.D.
4909 Nautilus Court N. Suite 208
Boulder, CO 80301-3242

(2) NAME OF NEW DIETARY INGREDIENT

The name of the new dietary ingredient is as follows:

DHA GOLD® Golden Algae

DHA refers to 4,7,10,13,16, 19-docosahexaenoic acid

OmegaTech, Inc.
4909 Nautilus Court N., Suite 208 Boulder, Colorado 80301-3242 (303) 381-8100 • Fax (303) 381-8181

(3) DESCRIPTION

The description of the new dietary ingredient is as follows:

DHA GOLD® Golden Algae is a golden to light orange powder or flake consisting of the heterotropically grown marine algae, *Schizochytrium* sp. The algae is grown in stainless steel fermentors under appropriate cGMPs. Natural tocopherols, ascorbyl palmitate, ascorbic acid, or other safe and suitable components are added for stabilization. The algae cells are dried using standard techniques common in the food industry. Labeling of the new dietary ingredient will specify that it should be used at up to 6 g/day to increase dietary intake of DHA.

(4) BASIS OF SAFETY OF DHA GOLD® Golden Algae

Summary

DHA GOLD® Golden Algae is a new dietary ingredient for use in dietary supplements. It is the product of a heterotrophic fermentation of the marine algae, *Schizochytrium* sp. *Schizochytrium* sp. is a thraustochytrid and a member of the Chromista kingdom (Stramenopilia) which includes the golden algae, diatoms, yellow-green algae, haptophyte and cryptophyte algae, and oomycetes. There are no reports of this organism producing toxic chemicals nor is it pathogenic. Chemical and biological analysis of the production strain confirmed the absence of the common algal toxins, domoic acid and *Prymnesium* toxin. Field tests by OmegaTech confirm the widespread occurrence of thraustochytrids in a typical marine food chain. Consumption by man of thraustocytrids, especially those of the genus *Schizochytrium*, is primarily through consumption of mussels and clams. Indirect consumption, through the marine food chain (fish and shellfish), is more widespread.

The safety of DHA GOLD® Golden Algae is based on the safety of the source organism, the safety of the oil soluble components of the source organism, i.e., the fatty acid and sterol components (detailed in a December, 1997 Monsanto DSHEA notification of SeaGold™ DHA-rich Oil, the oil component isolated from this algae), and a battery of classic toxicity studies conducted on the algae. Results of toxicology studies have been published or have been submitted for publication and were conducted by dietary administration or gavage of the source algae in laboratory animals and target species of food producing animals. Safety is further supported by the historical safe use of the algae as a commercial dietary ingredient in several commercial animal species.

Safety of the Source Organism

Schizochytrium sp. microorganisms are widespread and found throughout the world in marine environments. The literature indicates that thraustochytrids, especially those of the genus *Schizochytrium*, are regularly consumed as food by a wide range of

invertebrates. Field tests by OmegaTech confirm the widespread occurrence of the thraustoshytrids in a typical marine food chain, including the potential for direct consumption by man. Based on existing published and unpublished scientific data, there have never been any reports of toxic compounds produced by these microorganisms. Blue-green algae and dinoflagellates produce most of the toxic compounds produced by microalgae, and *Schizochytrium* sp. is in a separate kingdom from both of these types of microalgae. The two toxic compounds known to be produced in the Chromista (to which *Schizochytrium* sp. belongs) are largely restricted to two genera (domoic acid in *Pseudonitzschia* and prymnesin in *Prymnesium* spp.) which are in a separate class and phylum, respectively, from the thraustochytrids. No evidence of two toxic compounds produced in the Chromista, namely domoic acid and *Prymnesium* toxin, was found in *Schizochytrium* sp. algae using chemical and biological assays.

Safety of the Components of the Source Organism

The identified components present in DHA GOLD® Golden Algae have a demonstrated history of safe consumption. The lipid fraction of *Schizochytrium* sp. algae is comprised mainly of fatty acids and sterols. Fatty acids are found esterified to glycerol (tri- and diacylglycerides) and sterols (steryl esters) and may be present as free fatty acids. Sterols are found as steryl esters and free sterols. Beta-carotene was identified as the primary carotenoid component of the lipid fraction (Zeller et al., 2001).

All fatty acids in the oil phase of DHA GOLD® Golden Algae are components of a normal diet or normal metabolites of fatty acids. Recommended use levels will only increase the consumption of two component fatty acids, DHA and DPA(n-6), above that currently consumed from the diet. A comprehensive discussion on the safety of the fatty acid components present in the oil component of *Schizochytrium* sp. algae were detailed in a December, 1997 Monsanto DSHEA notification for SeaGold™ DHA-rich oil. Further support of the safety of DPA(n-6), a normal component of the human diet and component of human breast milk where it appears in a similar ratio to DHA as that found in oil derived from DHA GOLD® Golden Algae, is presented by Barclay et al. (2001).

The non-saponifiable fraction of the oil phase of DHA GOLD® Golden Algae consists primarily of squalene, sterols, and carotenoids. These components are all present in the food supply. At the proposed use level for a dietary supplement, the estimated consumption of sterols approximates the current consumption of sterols in the general population from other food sources and is likely smaller than some groups within the population such as vegetarians. A detailed discussion on the safety of the sterol components present in the oil component of *Schizochytrium* sp. algae were detailed in a December, 1997 Monsanto DSHEA notification for SeaGold™ DHA-rich oil.

The non-oil fraction of DHA GOLD® Golden Algae consists primarily of carbohydrates, proteins/amino acids, minerals and trace elements and vitamins, components commonly

found in the normal western diet and reasonably expected to be safe. Consumption of up to 6 g per day of DHA GOLD® Golden Algae may provide good sources of the vitamins, E, C, B_{12} and biotin.

Overview of Safety Studies Conducted on DHA GOLD® Golden Algae

i. Sub-Chronic Feeding Studies

DHA GOLD® Golden Algae from *Schizochytrium* sp. was administered in the diet to rats for at least thirteen weeks. The algae was administered in the diet to groups of twenty male and twenty female Sprague-Dawley derived rats to provide dosages of 0, 400, 1500 and 4000 mg/kg/day for at least 13 weeks. Untreated controls received basal diet only. An additional group of twenty males and twenty females received rodent diet mixed with fish oil (Arista) to provide a target dosage of 1628 mg/kg/day, an amount of fat comparable to that received by rats administered the highest dose of the algae.

There were no treatment-related effects in clinical observations, body weights or weight gains, food consumption, hematological or urinalysis values, gross necropsy findings or organ weights. The only treatment-related changes in clinical chemistry parameters were decreases in high-density lipoproteins (HDL) and cholesterol in the algae and fish oil groups when compared to the untreated controls. These changes were expected based on the polyunsaturated fatty acid content of dried algae and fish oil. There were no microscopic findings suggestive of toxicity. Periportal hepatocellular fat vacuolation (accumulation of fat) was observed only in the livers of female rats in both the algae (all dosages) and fish oil groups. This finding was expected given the higher fat content of both the algae and fish oil diets compared to the basal diet fed to the untreated controls. A slight increase in the incidence, but not severity, of cardiomyopathy was observed only in the 4000 mg/kg/day algae males. This finding was not considered adverse because cardiomyopathy occurs spontaneously in rats, and especially male rats of the Sprague-Dawley strain when fed high levels of fat. Since cardiomyopathy does not develop in other species including primates fed high fat diets, its occurrence in rats is considered to have little relevance to human health.

This study demonstrates that administration of DHA GOLD® Golden Algae does not produce any treatment-related adverse effects in Sprague-Dawley rats at dosages up to 4000 mg/kg/day for 13 weeks. (Hammond et al., 2001a)

ii. Developmental Toxicity Evaluation in Rats and Rabbits

The developmental toxicity of DHA GOLD® Golden Algae from *Schizochytrium* sp. was assessed in Sprague-Dawley-derived rats (25 per group provided dried algae in the diet at 0.6, 6.0 and 30% on gestation days [GD] 6-15 and in New Zealand White Rabbits, (22 per group, dosed with dried algae at levels of 180, 600 and 1800 mg/kg/day by oral gavage on GD 6-19). Fish oil was used as a control at dose levels to provide an equivalent amount of fat to that received by the high dose rabbits. Maternal food consumption, body weights and clinical signs were recorded at regular intervals

throughout these studies. Animals were sacrificed on GD 20 (rats) and GD 29 (rabbits) and examined for implant status, fetal weight, sex and morphologic development. No clinical signs of toxicity were observed. Maternal exposure to dried algae during organogenesis did not adversely affect the frequency of postimplantation loss, mean fetal body weight per litter, or external, visceral or skeletal malformations in either the rat or the rabbit.

In the rats, neither maternal nor developmental toxicity was observed at any dietary concentration of DHA GOLD® Golden Algae. Thus 22 g/kg/day of the algae administered in the feed to pregnant rats during organogenesis was the NOAEL (no observed adverse effect level) for both maternal and developmental toxicity.

Developmental toxicity was not observed at any algae dose level in the rabbit. Based on the results of this study, the NOAEL for maternal and developmental toxicity was 1800 mg/kg/day. (Hammond et al., 2001b)

iii. Single Generation Rat Reproduction Toxicity

The reproductive toxicity of DHA GOLD® Golden Algae from *Schizochytrium* sp. was examined in Sprague-Dawley-derived rats Crl:CD®(SD)BR (30 per sex per group) provided algae in the diet at concentrations of 0, 0.6, 6.0 and 30%. These dietary levels corresponded to overall average dosages of approximately 400, 3900 and 17800 mg/kg/day for F_0 males (pre-mating) and 480, 4600 and 20700 mg/kg/day for F_0 females, respectively. Prior to mating, males and females of the F_0 generation were treated for 10 weeks and 2 weeks, respectively. Treatment of males continued throughout mating and until termination (approximately 3 weeks after mating). Treatment of the females was continued throughout gestation and through lactation day 21. The females were killed after raising their young to weaning at 21 days of age. Food consumption was measured weekly throughout the study (except during mating) and body weights were recorded at least weekly during premating, gestation and lactation. Reproductive parameters including estrus cycle duration, mating performance, fertility, gestation length, parturition and gestation index were evaluated. Litter size, and offspring body weights were recorded, offspring viability indices were calculated, and physical development (vaginal opening and preputial separation) was assessed for the F_1 generation. All adult F_0 and F_1 animals were subjected to a detailed necropsy.

The DHA GOLD® Golden Algae treatment had no effects on estrus cycles or reproductive performance including: mating performance, fertility, gestation length, parturition or gestation index. Litter size, sex ratio and offspring viability indices were similarly unaffected and there were no effects of dried algae treatment to the physical development of F_1 animals. (Hammond et al., 2001c)

iv. Mutagenicity Studies

A series of studies to assess the genotoxic potential of DHA GOLD® Golden Algae from *Schizochytrium* sp. were performed. All *in vitro* assays were conducted with and without

mammalian metabolic activation. DHA GOLD® Golden Algae was not mutagenic in an Ames reverse mutation assay using five different *Salmonella* histidine auxotroph tester strains. Mouse lymphoma suspension assay methodology was found to be inappropriate for this test material because precipitating test material could not be removed by washing after the intended exposure period and the precipitate interfered with cell counting. The AS52/XPRT assay methodology was not subject to these problems and algae was tested and found not to be mutagenic in the CHO AS52/XPRT gene mutation assay. Algae was not clastogenic to human peripheral blood lymphocytes in culture. Additionally, algae did not induce micronucleus formation in mouse bone marrow *in vivo* further supporting its lack of any chromosomal effects. Overall, the results of this series of mutagenicity assays, combined with the rodent and rabbit studies cited above, support the conclusion that DHA GOLD® Golden Algae does not have any genotoxic potential. (Hammond et al., 2001d)

Availability of DHA in DHA GOLD® Golden Algae

Availability of dietary DHA when administered in the form of DHA GOLD® Golden Algae was evaluated in swine and rats. Nutritional availability of dietary DHA was assessed by the dose responsiveness of rat and swine tissues to varying levels of *Schizochytrium* sp. algae in their diets. In one study, female and male rats were fed whole-cell *Schizochytrium* sp. algae for 13 weeks providing approximately 32, 324 and 1440 mg DHA/kg body weight/day. The fatty acid content of rat sera and brain tissue was analyzed at the end of the 13-week period. In a second study, weanling male pigs were fed *Schizochytrium* sp. algae for 120 days at levels providing 114 mg DHA/kg/day and their brain tissue fatty acids were then quantified.

The sera data from the rat study indicated excellent availability of the fatty acids in the algae. Swine data also support ready availability of DHA from algae. In summary, these studies demonstrate that DHA content of tissues increases in rat and swine when DHA GOLD® Golden Algae is administered into the diet. (Barclay et al., 2001)

Historical Safe Use in Target Animal Species

DHA GOLD® Golden Algae from *Schizochytrium* sp. have been utilized in aquaculture applications, including enrichment of DHA in *Artemia* and rotifers used to feed larval fish and shrimp (Barclay and Zeller, 1996; Luizi et al., 1999). OmegaTech commercialized a product for aquaculture applications (HUFA2000, a spray-dried form of *Schizochytrium* sp. algae) which has been successfully utilized for over five years with no adverse effects in shrimp larvaculture and finfish (red seabream, Japanese flounder) culture. Use of DHA GOLD® Golden Algae from *Schizochytrium* sp. in these applications promotes larvae survival and growth. Studies have also been performed in juvenile mussels, *Mytilus galloprovincialis*, fed diets of spray-dried algal products, which included *Schizochytrium* sp. algae (Docosa Gold). Mussels fed dried *Schizochytrium* sp. algae as a partial replacement of live microalgae (*Spirulina platensis* or *Hematococcus pluvialis*) grew significantly faster than mussels fed a full live algal ration. Also, mussels

fed diets containing dried algae derived from *Schizochytrium* sp. grew significantly faster than mussels fed an equal ration of living Tahitian *Isochrysis galbana*.

DHA GOLD® Golden Algae from *Schizochytrium* sp. produced by fermentation is Generally Recognized as Safe (GRAS) for use as a feed ingredient incorporated into the feed rations of laying hens and broiler chickens at up to 4.3% of 2.8%, respectively (Abril, et al., 2000). Eggs containing up 2.5-5.0 times the DHA content of regular market eggs can be produced using *Schizochytrium* sp. algae as an animal nutritional food supplement. These eggs have been commercialized in Europe since 1996 and in the U.S. since 1998 under the Gold Circle Farms® brand. Additional references regarding the use of *Schizochytrium* sp. algae have been described in the literature for use in poultry applications (Herber and Van Elswyk, 1996; Herber-McNeill and Van Elswyk, 1998) poultry eggs and meat applications (Abril and Barclay, 1998; Barclay et al., 1998, Zeller et al. 2001), and for use in enriching swine and dairy products.

Laying Hen Study

A target animal safety trial with laying hens was conducted using DHA GOLD® Golden Algae from *Schizochytrium* sp. at dose levels of 165, 495, and 825 mg DHA/hen/day. Each treatment consisted of 64 laying hens divided into eight replicates (cages) per group for a total of 320 animals on study. As required by FDA laying hen target animal safety protocols, all of the hens were preconditioned for one month prior to the start of dosing period by feeding a basal commercial type layer feed. Body weights, food conversion, egg production, egg weight, shell thickness, and interior quality was measured at the end of each of the four months during the dosing period. Eggs were also collected and analyzed at the end of months 2 and 4 for their weight, shell thickness, interior egg quality, and fatty acid profile. At the end of the 4-month dosing period, terminal sacrifices were conducted and two randomly selected hens from each dose level and replicate were evaluated for hematological and histopathological changes. Hematological analyses included the following: red blood cell count, hematocrit, differential leukocyte count and hemoglobin. As dietary omega-3 fatty acids are known to decrease platelet reactivity, blood-clotting time was also determined. Gross necropsy was completed on all layers found dead during the trial or killed for scheduled evaluation. Weights were determined for the following organs: liver, kidney, heart, bursa of Fabricus, brain, spleen, thymus, bone marrow, and ovaries. Tissues were collected for histopathology, preserved, and evaluated. Breast tissue samples were evaluated for fatty acid profile by gas chromatography. Consequence of experimental diets was determined via statistical analysis of feed consumption/efficiency, egg production, egg weight, egg quality, body weight, organ weight, and histopathology.

There were no significant differences in any of the organ weights measured and there were no significant differences in the feathering score between any of the treatments. The results of the histopathological examination also indicated that no alterations could be observed in the tissues examined that would differentiate between treatment groups. There were also no significant differences between treatments for any of the hematological analyses.

It was concluded, based on results from this study, that DHA GOLD® Golden Algae from *Schizochytrium* sp., is safe as a feed ingredient for laying hens at 3040 mg/kg/day dried algae delivering approximately 532 mg DHA/kg/day. (Abril et al., 2000)

Broiler Chicken Study

A target animal safety trial with broiler chickens was conducted with two thousand two hundred and forty birds, sexed at day of hatch, wingbanded, and randomly assigned to one of four dietary treatments. In addition to a control broiler ration, dietary treatments of DHA GOLD® Golden Algae from *Schizochytrium* sp. delivered 82, 240, and 408 mg DHA/bird per day. Each dietary treatment contained 560 broilers divided among eight replicates (n=70; 35 males; 35 females). All rations were pelletized for feeding to the birds. Group body weights for each pen were determined on days 0, 21, and 49 of the feeding trial. Feed consumption was evaluated for each pen on days 21, 42, and 49 of the trial and used to determine feed efficiency for feeding periods 0-21 days and 0-49 days. On days 4 and 49, birds (n=2 per replicate) were bled for hematological analyses and sacrificed for histopathologic evaluation. Hematological analyses included the following: red blood cell count, hematocrit, differential leukocyte count, and hemoglobin. As dietary n-3 FA are known to decrease platelet reactivity, blood clotting time was also determined. Gross necropsy was completed on all broilers found dead during the trial or killed for scheduled evaluation. Weights were determined for the following organs: liver, kidney, heart, bursa of Fabricus, brain, spleen, thymus, bone marrow, and ovaries. Tissues were collected for histopathology, preserved, and evaluated. Breast samples were evaluated for fatty acid profile by gas chromatography. Consequence of experimental diets was determined by statistical analysis of feed consumption/efficiency, body weight, organ weight, and histopathology.

The results of this study indicate that there was no effect of treatment level on any of the evaluated broiler growth performance measures. There was no significant difference between treatment level regarding weight gain, feed intake, or feed conversion. There was no significant difference between treatments on organ weight for the liver, kidney, heart, bursa of Fabricus, brain, spleen, thymus, bone marrow, or ovaries. The histopathological examination also indicated that no alterations could be observed in the tissues examined that would differentiate between treatment groups. There was no significant difference between treatment for any of the hematological analyses conducted.

It was concluded, based on results from this study, that DHA GOLD® Golden Algae from *Schizochytrium* sp., is safe as a feed ingredient for broiler chickens at 2331 mg/bird/day dried algae delivering approximately 408 mg DHA/bird/day.

Swine Study

A target animal toxicology study was conducted in swine to determine the potential toxicity of DHA GOLD® Golden Algae from *Schizochytrium* sp. In this study dried algae was administered in the diet to groups of castrated male growing pigs (mixed commercial

breeds Land Race & Large White) reared from early weaned to approximately 250-270 pounds. Over the course of the 120-day study, animals were fed *ad libitum* four treatment diets each designed to optimize weight gain over the growing cycle. *Schizochytrium* sp. algae was incorporated into the diet of the first treatment group at a level delivering 2.680 kg algae per pig over the course of 120 days (a constant, whole-life exposure) equating to 598 g DHA per pig (or approximately 511 mg algae/kg/day or 114 mg DHA/kg/day). *Schizochytrium* sp. algae was incorporated into finisher diets only (administered over the last 42 days of the growing cycle) to treatment groups 2, 3, and 4 delivering 1.169, 3.391, and 5.746 kg algae per pig (261, 756, and 1281 g DHA per pig). These levels represent approximately 1, 3, and 5 times the anticipated commercial dose and were delivered in a feeding strategy designed to mimic commercial use.

Results of this animal study demonstrated no statistically significant treatment-related effects in clinical observations, body weights, food consumption, mortality, hematological values, gross necropsy findings, organ weights or histopathology. The only treatment-related changes were higher weight gain and feed conversion efficiency, anticipated results based on the increased fat content in the experimental algae diets.

In summary, this study demonstrates that administration of dried *Schizochytrium* sp. algae (at up to five times the anticipated commercial dose) does not produce any treatment-related adverse effects in commercial strains of swine. (Abril et al., 2001)

Manufacture of DHA GOLD® Golden Algae

DHA GOLD® Golden Algae is produced in a fermentation process using an algae from the genus *Schizochytrium* sp. The algae are grown via a pure culture heterotrophic fed-batch fermentation process. The organism used is an improved strain of the original wild-type culture (*Schizochytrium* sp. ATCC 20888). The improved strain was derived using a classical mutagenesis-screening program, which employed well-accepted techniques commonly used in industrial microbiological strain improvement programs. Natural tocopherols, ascorbyl palmitate, ascorbic acid, (or other safe and suitable components) are added to the fermentation broth prior to drying, for stabilization. Conventional food product drying techniques are employed to produce a golden free-flowing powder. All aspects of the production of DHA GOLD® Golden Algae are conducted under appropriate cGMP's.

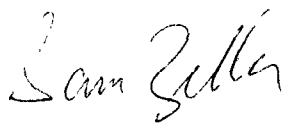
Proposed Specification for DHA GOLD® Golden Algae Dietary Supplement Grade

Test	Specification	Test Method
DHA Content (%)	18 minimum	OT-ANM-01-009R
Heavy Metals (ppm)	<20	FCC IV
Arsenic (ppm)	3 maximum	FCC IV
Lead (ppm)	2 maximum	FCC IV
Total Aerobic Microbial Count	<3000 cfu/g	USP <2021>
Combined Yeasts & Mold	<300 cfu/g	USP <2021>
Eschericha coli	absent in 10 g	USP <2021>
Salmonella	absent in 10 g	USP <2021>
Staphylococcus aureus	absent in 10 g	USP <2021>

Conclusion

The reasonable expectation of safe use of DHA GOLD® Golden Algae as a dietary supplement at dietary intakes up to 6 g/day is based on the information summarized above and further supported by a 1997 Monsanto DSHEA notification of SeaGold™ DHA-rich oil. The safety of this product is based on the safety of the source microorganism. *Schizochytrium* sp. occurs widely in the marine environment and is an indirect component of the human food chain through consumption of fish or other marine animals that feed on *Schizochytrium* sp. There have never been any reports of toxic compounds produced by this organism. The major components present in the algae, namely the fatty acids and sterols, have been identified to be present in the human food chain. The safety of these components is based on their history of safe use in food, the small quantities expected to be consumed, extensive knowledge of their metabolism, published safety studies and the absence of reports of toxicity. A battery of classical toxicology studies were conducted directly on DHA GOLD® Golden Algae derived from *Schizochytrium* sp. Results of safety studies establish that dried algae was not mutagenic in bacterial and mammalian test systems and were not teratogenic in a rat dietary teratology study or in a rabbit gavage teratology study. There was no evidence that dried algae produced by fermentation of *Schizochytrium* sp. interfered with reproductive performance or progeny development in a rat one-generation dietary reproduction study. Results of sub-chronic and whole-life exposure to rats, swine, laying hens and broiler chickens demonstrate lack of toxicity. *Schizochytrium* sp. algae has been used commercially for over five years in aquaculture applications and has been used commercially to enrich DHA content in eggs by feeding algae to laying hens. Egg production and egg qualities are sensitive indicators of toxicity and/or nutritional imbalances in poultry. The wide spread commercial use of this algae to enrich eggs in DHA in more than a dozen countries is further evidence of safety of DHA GOLD® Golden Algae over extended periods.

Respectfully submitted,



Sam Zeller, Ph.D.
Associate Director, Regulatory Affairs
OmegaTech Inc.

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